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CURRENT DEFICIENCEIES IN SCHEDULE-Y

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ABSTRACT
To investigate "up-to-date" and "age-appropriate" indicators of preschool vaccination status and their implications for vaccination policy. The authors analyzed medical records data from the Baltimore Immunization Study for 525 2-year-olds born from August 1988 through March 1989 to mothers living in low-income Census tracts of the city of Baltimore. While only 54% of 24- month-old children were up-to-date for the primary series, indicators of up-to-date coverage were consistently higher, by 37 or more percentage points, than corresponding age-appropriate indicators. Almost 80% of children who failed to receive the first dose of DTP or OPV age appropriately failed to be up-to-date by 24 months of age for the primary series. Age-appropriate immunization indicators more accurately reflect adequacy of protection for pre schoolers than up-to-date indicators at both the individual and population levels. Age-appropriate receipt of the first dose of DTP should be monitored to identify children likely to be under immunized. Age-appropriate indicators should also be incorporated as vaccination coverage estimators in population-based surveys and as quality of care indicators for managed care organizations. These changes would require accurate dates for each vaccination and support the need to develop population-based registries.

KEYWORDS: vaccination, Baltimore, DTP, age-appropriate, pre schoolers.

INTRODUCTION
The Indian pharmaceutical industry is one of the fastest-growing sectors globally, contributing significantly to the nation's economy and public health. To regulate this vast and complex industry, the Drugs and Cosmetics Act, 1940 and Rules, 1945 were established to ensure that drugs marketed in India are safe, effective, and of good quality. Within these rules, Schedule Y serves as a vital component that outlines the **requirements and guidelines for clinical trials, approval of new drugs, and post-marketing surveillance.**

Initially introduced in **1988** and substantially amended in 2005, Schedule Y was revised to align with the Good Clinical Practice (GCP) standards and international norms such as those of the **International Council for Harmonisation (ICH), U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA).** The 2005 revision aimed to make the Indian regulatory framework more transparent, ethical, and globally acceptable. However, in the past two decades, the pharmaceutical landscape has changed dramatically, and the existing Schedule Y has not evolved correspondingly.

As a result, several deficiencies and shortcomings have become apparent, particularly concerning the regulation of modern drug development technologies, advanced clinical trial designs, and ethical considerations. The current framework often lags behind international best practices, posing challenges to researchers, regulators, and the pharmaceutical industry.

Overview of Schedule Y

Schedule Y primarily deals with the following areas:

- Requirements and guidelines for conducting clinical trials in India.
- Responsibilities of sponsors, investigators, and ethics committees.
- Data submission requirements for new drug approval.
- Import and manufacture of new drugs for clinical trials or marketing.
- Post-marketing surveillance and pharmacovigilance.

Major Deficiencies in Schedule Y

Outdated and Incomplete Coverage

The most prominent deficiency in Schedule Y is that it was designed at a time when drug discovery primarily focused on **chemical (small-molecule) entities**. Today, the pharmaceutical world has expanded to include **biological products, biosimilars, monoclonal antibodies, gene therapy, vaccines, cell-based therapies, and nanomedicines**.

Schedule Y provides **no comprehensive framework** for these complex biological products. For example:

- There are no specific guidelines for the **comparability exercises** required for biosimilars.
- **Gene and cell therapies,** which require unique ethical and safety considerations, are not clearly addressed.
- **Nano pharmaceuticals and personalized medicine** approaches are completely absent.

Thus, the lack of specific provisions for modern therapies leads to regulatory uncertainty and hinders India's ability to fully participate in global innovation.

Ambiguity in Clinical Trial Phases and Procedures

Although Schedule Y describes clinical trial phases, the definitions are **vague and overlapping.** It lacks clear instructions on:

- **Adaptive and seamless trial designs,** which have become standard in modern drug development.
- **Bridging studies** to extrapolate foreign clinical data to Indian populations.
- **Early termination criteria,** interim analyses, or real-world evidence integration

Because of this ambiguity, sponsors and ethics committees often interpret the rules differently, leading to delays, inconsistent approvals, and non-uniform implementation.

Ethical Oversight Deficiencies

While Schedule Y mandates approval from an **Ethics Committee (EC)** and informed consent from participants, there is **no uniform standardization** in the structure or functioning of these committees across India.

Key deficiencies include:

- Inconsistent training and accreditation of EC members.
- Variability in the independence and capability of institutional ethics committees.
- Lack of monitoring mechanisms for EC decisions.
- Limited protection for vulnerable populations such as children, pregnant women, and economically disadvantaged groups.

Additionally, Schedule Y provides **minimal guidance on compensation** for trial-related injuries or deaths. Although later notifications (2013, 2019) clarified compensation rules, these are **not integrated into Schedule Y,** leading to confusion and regulatory fragmentation.

Weak Post-Marketing Surveillance (Phase IV Studies)

Another serious deficiency lies in the **pharmacovigilance and post-marketing surveillance** system. Schedule Y briefly mentions Phase IV studies but does not:

- Specify the methodology or reporting requirements.
- Mandate structured safety data collection or risk management plans.
- Encourage active surveillance through databases or electronic medical records.

As a result, India lacks a robust mechanism for identifying long-term or rare adverse effects. Post-marketing safety largely depends on voluntary reporting, which is insufficient to ensure patient protection.

Lack of Digital Integration and Data Integrity Standards

Modern clinical research heavily relies on **electronic data capture (EDC), remote monitoring**, **and risk-based data management**. However, Schedule Y does not address:

- Digital record-keeping or e-signature validation.
- Electronic submissions for regulatory review.
- Data integrity, audit trails, or cybersecurity requirements.

This absence of digital regulation reduces India's compatibility with international data standards such as those set by the U.S. FDA's **21 CFR Part 11 or the EU Clinical Trials Regulation (CTR).**

Administrative and Procedural Inefficiencies

There are several operational limitations within Schedule Y's implementation:

- No defined timelines for approval of clinical trial applications (CTAs).
- Lack of clarity regarding the review process and decision hierarchy within CDSCO.
- Limited coordination between central and state authorities.

- Shortage of skilled personnel for scientific and technical evaluation.

These issues often lead to **delays and unpredictability** in the approval process, discouraging both domestic and international sponsors from conducting clinical trials in India.

Lack of Periodic Revision and Stakeholder Consultation

Unlike regulatory frameworks in the U.S., EU, or Japan, where guidelines are **periodically updated**, Schedule Y has not undergone a comprehensive revision since 2005. The absence of a formal mechanism for continuous improvement or stakeholder consultation results in a **stagnant regulatory system.**

Scientific innovation has far outpaced the existing guidelines, leaving Schedule Y unable to accommodate new methodologies such as

- **Real-World Evidence (RWE) studies.**
- **Artificial Intelligence (AI)–based trial designs.**
- **Decentralized or remote clinical trials.**
- **Adaptive licensing pathways.**

Comparison with International Regulatory Practices

Globally, regulatory agencies such as the **U.S. FDA, EMA, MHRA (UK),** and **PMDA (Japan)** continuously update their frameworks to integrate evolving technologies and ethical standards. They have established clear, transparent mechanisms for:

- Risk-based trial monitoring.
- Electronic data submission (eCTD).
- Rapid review and accelerated approval processes.
- Real-time pharmacovigilance databases.

India's Schedule Y, by contrast, remains **static and partly disconnected** from these developments. This limits the international recognition of Indian-generated data and discourages multinational collaborations.

The Need for Reform

The growing demand for high-quality, ethically sound clinical data makes it imperative that Schedule Y be **comprehensively revised**. A modernized Schedule Y should:

- Include **specific guidelines for biologicals, gene therapies, and biosimilars**.
- Clearly define the roles of sponsors, investigators, and ECs.
- Strengthen **pharmacovigilance** and post-approval safety monitoring.
- Introduce **digital submission systems,** data integrity standards, and e-governance.
- Ensure **regular review and alignment** with ICH, WHO, and OECD guidelines.

Such reforms would enhance India's regulatory credibility, protect human participants, and make the country a preferred destination for ethical and scientifically sound research.

Since the implementation of the New Drugs and Clinical Trials (NDCT) Rules in 2019, Schedule Y has been superseded and is no longer the governing regulation for clinical trials in India. Therefore, any deficiencies associated with Schedule Y are now historic and were addressed by the NDCT Rules, which aimed to bring India's clinical trial regulations in line with global standards.

Here are the primary deficiencies of the now-defunct Schedule Y that led to the creation of the NDCT Rules in 2019:

Clinical Trials

According to Schedule Y rule 122-DAA, a clinical trial is defined as "a systematic study of any new drug(s) in human subject(s) to generate data for discovering and/ or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/ or adverse effects with the objective of determining safety and/ or efficacy of the new drug."1 Clinical trial usually compares new treatment approaches with a standard one already available in the market. When a new product is studied, it is not known whether it will be useful, harmful or similar to the already available alternative.

The investigators determine both the safety and efficacy of the interventions by measuring individualized outcomes in the participants according to the research protocol prepared by the investigators and approved by regulators and ethics committee (EC). These clinical studiescan be sponsored by various agencies like pharmaceutical companies, academic centers providing medical education, voluntary groups, other organizations, etc.2

Phases of Clinical Trials

All new drug molecules have to undergo four phases of clinical trials in India, although Phase I is not mandatory in all cases. Each phase is covered in a sequence following strict guidelines to safeguard not only the health of the subjects of the trial but also for understanding the potential risks of the new drug molecule on the health of the patients who are going to consume them later. For new chemical entities discovered in India, clinical evaluation starts from phase I clinical trial.

These phase I trials are conducted to evaluate the pharmacological and metabolic actions of the molecule on its first use among humans.

Phase II trials observe the efficacy, dose response relationship, tolerance and adverse effects of the drug. Larger group of subjects (normally 200-300) with the targeted disease are included based upon very-welldefined inclusion and exclusion criteria.

On the other hand, phase III trials are the final step before the drug innovator can apply for marketing authorization. The number of subjects may range from several hundred to several thousand who are followed for a few years (2 to 5 years). Phase III trials mainly focus on the safety and efficacy of the molecule in diverse sub-groups with broader inclusion/ exclusion criteria.4 After Phase III trials, the drug is approved for marketing. Now is the time for the drug to be tested for its adverse effects in the wider population base. This is called the phase IV of the clinical trials where the pharmaceutical company looks for any adverse effects of their newly marketed product in the general population after it has been openly marketed. This exposure tests nearly all possible permutation and combinations of co-morbidity and concomitant medication.

Clinical Trials: Practical Challenges

The biggest barrier in the conduct and completion of a clinical trial is the hesitation in participation in the trials or a high drop rate after participation. The main reason for this is the unawareness ofthe existence and benefits of well-regulated clinical trials. There is a fear of unfair and unethical practices on the part of pharmaceutical companies and drug regulators. This fear is based on past experiences seen in the form of deaths and permanent injuries caused by new drug molecules during the conduct of clinical trials.

The recent example of a fatal incident which occurred in a Phase I clinical trial subjects enrolled by a French CRO in January, 2016 took the whole world by surprise and suspicion. When the incident was scrutinized, it was concluded that there were many mistakes on the part of researchers. The doses of the new drug were given in too quick a succession; there was a delay in interpretation of the adverse effects seen in the first case and as a result the others continued to receive the same drug for many more days and there were many inadequacies in the approval process as the compound being tested was no more effective than several others from the same family that had already been abandoned on the basis of poor efficacy.

In 2010, Central Drugs Standard Control Organization (CDSCO)started clinical trial inspection programs, based on guidance documents for inspection of the sites of conduct of clinical trials, but their implementation remained a major problem. In India, deaths seen in cases such as anticancer drug study in a hospital from Kerala and recruitment of children in a study at a hospital in New Delhi, 6,7 show the inadequacies in the working of the Institutional Review Boards/ Independent Ethics committees. Not only this, many shortcomings have come up in the 59th report of the Parliamentary Standing Committee on Health and Family Welfare on the part of Indian drug regulatory bodies. All of these are valid concerns and need to be dealt with. Much more is required to be done to prevent the unnecessary approval of clinical trials and new drugs under waiver clauses of the Schedule Y rules.8

Pharmacovigilance Program of India

When a new drug is exposed to larger masses during marketing, newer and unpredictable adverse effects come into picture. For the monitoring of such developments, Government of India launched the Pharmacovigilance Program of India (PvPI) in July 2010 through CDSCO. The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem."

The National Coordinating Center (NCC) of PvPI is located at Indian Pharmacopoeia Commission (IPC), Ghaziabad which provides all the technical support to the CDSCO office. Reports that are generated at adverse drug reaction (ADR) monitoring centers (AMC) are sent to the NCC which correlate, assess and then incorporate these reports into the pharmacovigilance database through vigiflow to the WHO's Uppsala Monitoring Center (UMC).8 In addition, ADRs from clinical trials, vaccination and other programs are also archived in the data bank for comprehensive records.

AIM AND OBJECTIVE

The primary aim is to analyze the historical context that led to a significant overhaul of India's clinical trial regulations. This analysis helps explain why the NDCT Rules, 2019, were necessary and what they were designed to achieve.

Key aims of this retrospective analysis include:

Identify gaps in patient safety

Understanding the failures of Schedule Y in protecting participants, such as issues with informed consent and adverse event reporting, to highlight the need for more robust safeguards.

Evaluate ethical lapses

Investigating past ethical misconduct, including the exploitation of vulnerable populations and conflicts of interest within ethics committees, to provide justification for stricter ethical mandates.

Assess regulatory inefficiency

Reviewing the bureaucratic hurdles, delays, and inconsistent oversight under Schedule Y to explain why a more streamlined and transparent system was required.

Learn from previous failures

Using the past to inform future policy. By studying how India's clinical trial industry plummeted following the regulatory backlash of 2013–2015, stakeholders can understand the delicate balance required between strong oversight and operational feasibility.

DISCUSSION

India's pharmaceutical industry has grown into one of the largest globally, ranking among the top producers of generic medicines and vaccines. However, despite these achievements, the regulatory framework that governs clinical trials and new drug approvals—principally Schedule Y of the Drugs and Cosmetics Rules, 1945—remains inadequate for contemporary challenges.

Schedule Y serves as the legal guideline for conducting clinical research, describing requirements for various trial phases, ethical oversight, and marketing authorization. Its most recent major amendment in 2005 aimed to align Indian standards with international norms such as ICH-GCP (International Conference on Harmonisation – Good Clinical Practice). Since then, however, the field of drug development has witnessed revolutionary changes— ranging from biotechnological innovations, personalized medicine, and artificial intelligence in clinical trials, to global harmonization and digitization of regulatory processes.

Unfortunately, Schedule Y has not kept pace with these changes. Consequently, there exist numerous regulatory deficiencies that hinder the efficiency, transparency, and international credibility of India's clinical research environment.

This discussion provides a comprehensive analysis of these deficiencies, their underlying causes, implications for the pharmaceutical sector, and potential directions for reform.

Historical Perspective of Schedule Y

Schedule Y was first introduced in 1988, focusing primarily on ensuring basic ethical conduct and data validity in clinical trials. The 2005 amendment was a landmark reform—it expanded the document to cover:

- Definitions and classification of clinical trial phases (I–IV),
- Requirements for Ethics Committee approvals,
- Provisions for informed consent, and
- Data submission requirements for new drug approval.

While the 2005 revision was progressive for its time, it has remained largely static in a rapidly evolving scientific and regulatory environment. Emerging concepts such as biologics, biosimilars, cell and gene therapies, digital health technologies, adaptive clinical designs, and global data integration were not envisioned in the original framework.

This stagnation has resulted in structural and procedural deficiencies that now impede India's ability to function as a globally competitive research hub.

Implications of These Deficiencies

1. **Reduced Global Acceptance**
   Clinical trial data generated in India often face scrutiny abroad due to regulatory and ethical discrepancies.
2. **Loss of Investment**
   Multinational sponsors prefer regions with predictable and transparent regulations.
3. **Ethical Concerns**
   Weak participant protection mechanisms affect public trust.

Data Quality Issues

Absence of digital validation reduces reliability and reproducibility.

Innovation Barriers

Emerging technologies like AI, precision medicine, and gene therapy lack regulatory pathways.

Fragmented Oversight

Inconsistent application of rules between central and state authorities leads to inefficiency.

Future Prospects

If these reforms are implemented, India could evolve into a global leader in clinical research and innovation. Harmonization with ICH, WHO, and OECD standards will not only enhance public health outcomes but also boost international confidence in Indian clinical data.

Furthermore, modernization of Schedule Y will align it with India's Digital Health Mission and Make in India initiatives—creating a robust environment for scientific growth and ethical research.

Specific deficiencies under Schedule Y

Ethical violations

In the years leading up to the 2019 rules, there were widespread concerns over unethical clinical trials. Reports detailed poor patient informed consent, lack of oversight by Ethics Committees, and the selective exploitation of vulnerable, low-income individuals.

Insufficient compensation

Schedule Y's compensation framework for trial-related injuries or death was widely considered inadequate and confusing. The process was often opaque and involved lengthy legal battles for victims and their families.

Inconsistent and slow reporting

Schedule Y had timelines for reporting Serious Adverse Events (SAEs) that were inconsistent with international standards. This meant foreign regulators would be aware of an issue before their Indian counterparts, creating confusion, especially in multinational trials. The guidelines also did not specify expedited reporting requirements for Suspected Unexpected Serious Adverse Reactions (SUSARs).

Regulatory delays
Cumbersome, multi-tiered approval mechanisms caused significant delays in getting new drugs and clinical trials approved. The unpredictable timelines hindered growth in the Indian clinical research sector.

Unaddressed ethical concerns
Issues such as the over-representation of impoverished populations in trials, lack of transparent trial registration (positive trials were more likely to be registered), and collusion between some drug companies and doctors were not adequately addressed.

Regulatory incompetence
A 2012 parliamentary committee report criticized the Central Drugs Standard Control Organization (CDSCO) for prioritizing the drug industry over consumer protection. This skewed priority led to numerous reported ethics violations.

How the NDCT Rules, 2019, addressed the issues
The New Drugs and Clinical Trials Rules were an ambitious effort to overhaul the regulatory framework.

Key changes included
Streamlined approval process
The new rules established clear, predictable timelines for trial approvals, including a "deemed approval" provision if the Drugs Controller General of India (DCGI) does not communicate an objection within a specified period. This helps reduce delays.

Standardized ethics review: The NDCT Rules introduced stricter regulations for Ethics Committees (ECs), mandating that all ECs be registered with a central authority. Thisstandardized the review process and aimed to increase the independence and competence of EC members.

Clearer compensation rules
The rules defined a transparent compensation structure for trial-related injury or death, with specific formulas for calculation. They also mandated that medical management be provided to the patient for as long as required.

Increased patient protection
The regulations emphasized patient safety, rights, and informed consent. They also included provisions for mandatory registration with the Clinical Trials Registry of India (CTRI) for all clinical trials, improving transparency.

Alignment with global standards
The rules addressed many of the inconsistencies with international pharmacovigilance practices, aligning India more closely with global norms and potentially improving India's role in multinational trials.

Persistent criticisms and deficiencies in the NDCT Rules
While a significant improvement, the new rules are not without their own flaws:

Continuing ethical concerns
Some critics argue the NDCT rules prioritize market interests over participant safety. The provision allowing waivers for local clinical trials for drugs approved in certain developed countries was met with criticism for potentially sidelining India's ethnic diversity.

Vague language
Some rules were drafted with ambiguous language, creating new problems and impeding progress. For instance, the exact role and function of ECs in certain scenarios are not clearly defined.

Inadequate bridging trial provisions
The rules have been criticized for not adequately addressing the need for bridging trials to account for India's vast ethnic diversity, especially when waiving local trials.

Manipulation potential
Proving a trial-related injury for compensation can still be problematic and susceptible to manipulation, even with clearer rules.

Ethics committee independence
While aiming to regulate ECs, critics question if the rules truly address the underlying issue of EC independence from sponsor influence.

RYGBP has become one of the most common bariatric procedures. However, long-term nutritional outcome data remain scarce, and, aside from a few published expert recommendations, there are no guidelines regarding the optimal postoperative nutritional follow-up. The aim of this study was to improve our knowledge of the nutritional consequences of RYGBP, because of potential complications related to development of nutritional deficiencies such as neurologic dysfunction for vitamin B-12 deficiency.

Our main observations are as follows. 1) Standard multivitamin supplementation is not sufficient to prevent nutritional deficiencies after RYGBP. Indeed, almost 60% of our patients required one or more nutritional supplements 6 mo after surgery, with virtually all patients needing them after 2 y. 2) The prevalence of vitamin D and calcium deficiency increases significantly with the length of the Roux-en-Y limb. 3) Proper postoperative nutritional substitution can become a burdensome and expensive treatment, which may challenge a patient's compliance considerably.

The reported incidence of specific deficiencies after RYGBP varies widely in the current literature: between 10% and 50% for vitamin B-12 and iron and between 0

and 40% for folic acid. Hypovitaminosis D with secondary hyperparathyroidism was found in up to 80% of patients both pre- and postoperatively. No data are available for vitamins B-1 and B-6, magnesium, and zinc. However, most authors report the incidence of specific deficiencies at different time points after surgery, without considering the number of patients who will require any substitutive treatment during follow-up. In addition, some authors prescribe a multivitamin supplement immediately after RYGBP and others do not, potentially confounding the data. Finally, the time points at which patients are studied vary among studies, and yet, as exemplified by the present data, the prevalence of nutritional deficiencies increases with time. We chose here to report the proportion over time of patients receiving one or more nutritional supplements. Because these supplements were prescribed according to strict guidelines on the basis of regular biologic measurements, we believe that these data provide an accurate picture of the clinical importance of this problem over the period under study. By reporting the mean number of supplements prescribed for each patient, our study is also the first to illustrate the burden of nutritional substitution.

Despite some limitations inherent to the retrospective design of this study, our data stress the fact that oral and/or parenteral nutritional supplementation can become a potential problem for patients. Indeed, they demonstrate that a standardized multivitamin supplement with asingle pill per day will probably not meet the needs of the vast majority of patients. Taking several pills a day raises the problem of adherence to treatment. The cost of treatment can be another barrier to adequate compliance. Our estimates show that 2 y after RYGBP, a patient will have to spend on average $35 per month for his or her nutritional supplements, an amount high enough to impair compliance in a significant proportion of patients in countries in which health insurance companies do not cover these costs. This situation is well illustrated by a study reporting that in a group of 348 patients treated by RYGBP, only 33% complied with the multivitamin regimen throughout the study period. This dramatically low adherence rate suggests that appropriate compliance should regularly be assessed and encouraged during the postoperative follow-up. Finally, costs related to extensive biologic nutritional assessment are also high, averaging $360 per patient per sample at our center or $2100 for the 6 blood samples obtained during the entire follow-up period. Although the cost-benefit ratio of this follow-up should be formally evaluated, our data stress the need for a carefully planned postoperative follow-up, taking into account potential benefits to the patients as well as health care–related costs.

Because all patients received a multivitamin supplement between months 1 and 6 after RYGBP, the real incidence of nutritional deficiencies during this period probably cannot be extrapolated from the present data. However, prescribing a multivitamin supplement after RYGBP is a commonly used procedure, and therefore these results may be a better reflection of what would be found in other clinics using similar treatment plans. We also did not seek information about the preoperative nutritional status of our patients, and deficiencies recorded during follow-up may possibly represent problems existing before the surgical procedure. However, most deficiencies occurred after the sixth postoperative month, suggesting that they were not present before surgery.

In consideration of the high prevalence of nutritional deficiencies, the relative rapidity of their appearance after RYGBP, the lack of effectiveness of multivitamin supplementation, and the high cost of the above-mentioned postoperative follow-up, an achievable alternative to our follow-up schedule and treatment plan would be to prescribe vitamin B-12, iron, calcium + vitamin D-3, and folic acid supplements in sufficient amounts to all patients after RYGBP. A pragmatic approach of prescribing a double dose of a multivitamin is sometimes used; however, the effectiveness of this approach has not yet been fully demonstrated. Therefore, the development of a single “multi-pill” or injection containing appropriate doses of vitamin B-12, iron, calcium + vitamin D-3, and folic acid would facilitate compliance and reduce costs; research to determine the proper dosage and route of administration of this type of medication should be encouraged. With such a regimen, our data suggest that nutritional assessments performed every 6 mo would be adequate to both detect less frequent deficiencies such as those of vitamins B-1 and B-6, zinc, or magnesium and monitor the efficacy of treatment.

RYGBP has become one of the most commonly performed bariatric procedures. Our data demonstrate that after surgery routine supplementation with a standardized multivitamin preparation alone does not prevent the frequent occurrence of nutritional deficiencies. We therefore suggest that rigorous postoperative follow-up should be implemented in all patients to detect the most frequent of these deficiencies, which include deficiencies of vitamin B-12, iron, calcium, 25-hydroxyvitamin D, and folic acid. Given the prevalence and clinical importance of this problem, prospective studies should be performed to establish formal guidelines for the nutritional care of these patients.

We express our deep gratitude to François Pralong, who offered his help by revising the manuscript.

The author's responsibilities were as follows—CG: collected and analyzed data, interpreted results, and wrote the manuscript; MS: participated in data collection and revised the manuscript; RG: revised the manuscript; and VG: participated in data collection, interpreted results, and wrote the manuscript. None of the authors had a personal or financial conflict of interest.

This DCE study was designed to estimate the relative importance and preferences for different aspects of the growth hormone injection device's use and handling. This patient preference study is the first study that we are aware of to evaluate patient preference for GH injections in this way. The strength of this DCE enabled an exploration of preferences relating to alternative options for delivery of r-hGH which are not currently available.

The focus of the study was on the degree to which each attribute contributed to the desirability of a pen device, rather than whether a particular device configuration would actually be used (or would be more preferable compared to existing options). This study, involving children, adolescents (and their caregivers) and adults yielded several results of interest. Overall, respondents indicated a clear preference for a less frequent injection schedule rather than daily injections (i.e., a preference for weekly, bi-monthly or monthly injections). This attribute was more important relative to others.

The study also included a separate exercise looking at the uptake of whether the participant would choose to switch from their current daily pen device, if given the chance, to a less frequent injection schedule. The results show that the vast majority of respondents would switch to a less frequent injection administration (weekly, biweekly or monthly, although there appeared to be slightly less support for a schedule given once every two weeks).

The results for each age category (children, adolescents and adults) are generally consistent. However, results indicate that adolescents showed a greater tendency to switch to a less frequent injection schedule compared to the adult and Pediatric cohorts. This is perhaps unsurprising, as evidence suggests that adherence to treatment in this age group reduces. Hence, the availability of an injection pen which requires only a once-weekly injection, or even fewer administrations, could offer patients a valuable option which could improve adherence and persistence, with potential clinical implications for improved growth outcomes.

The lower preference for a less frequent injection schedule seen in our adult cohort is aligned with a recent publication which also reported that adult patients were less likely to switch to a weekly injection schedule. The Amereller study suggests that if patients were provided with additional information regarding the efficacy and safety of a newly introduced product, patients may be more willing to switch when they are offered a choice between weekly and daily injection schedules. DCE studies have some limitations. The potential for hypothetical bias is a general concern. Choices involving hypothetical treatments do not have the same clinical, financial and emotional consequences of experiencing the actual treatment. Hence, differences may arise between patients stated and actual choices. In this study, all respondents had considerable experience treating their GHD with daily injections; none of the respondents had experience or knowledge of alternative injection schedules.

All recruited participants were enrolled exclusively from clinics in the US, and while treatment for GHD is standard across different countries and regions, and therefore bias should be minimal, in an ideal scenario, patient preferences from other countries should also have contributed to these results. While patients in transition were excluded from this study, future research should explore the experiences of these patients.

Whilst the authors identified the attributes via internal consultation and previous research, the attributes identified and evaluated had not been robustly researched via a literature review and this could also be considered a limitation of the study. However, it is unlikely that a key attribute had been omitted. Attributes in DCE studies are always pre-defined and therefore it is possible a more relevant attribute may have been missed, but this is a limitation of all DCE studies.

One strength of the recruited sample is that since all respondents had participated in a broader clinical study we can be assured that everyone had been confirmed with a diagnosis of GHD. All participants in the clinical study participated in the conjoint analysis, with no drop outs – suggesting completion was not burdensome or challenging.

The attributes and scenarios applied in this study were tested in a set of 10 pilot interviews, during which respondents completed the online DCE exercise while a moderator observed them completing the exercise via screen share. During and after the exercise, the moderator asked the respondent targeted questions to ensure they understood the content and options presented. The results of this pilot study indicated that the attributes and scenarios were tangible and easily understood by respondents, so it is unlikely to have led to misunderstandings or lack of comprehension which may have led to varying interpretations of the data.

In conclusion, the voice of the patient and patient preferences regarding novel and different treatment options is becoming increasingly important to many stakeholders, in particular regulators who are interested in how these studies may best support the benefit/risk analysis of a new drug. In this study, the DCE was successful in evaluating the trade-offs and preferences patients with GHD and caregivers (dyads), when appropriate, were willing to make amongst injection pen attributes. The findings from this study suggest that a less frequent injection schedule is the most preferred and important attribute for patients with GHD. Less frequent injection schedules may be an important factor to improve compliance in this therapy area, which would lead to improved outcomes in the longer term. A recommended next step would be to conduct a randomized clinical trial, and ideally a real-world data

study, to scientifically and robustly determine the clinical implications of a less frequent injection regimen.

These results do not support the hypothesis that a defect in the NPY system is mediating the decreases in intake during zinc deficiency. Concentrations of NPY in the PVN and NPY mRNA in the ARC were higher in Zn0 than in Zn/ rats. This difference appeared to be related more to decreased food intake than zinc deficiency because pair-fed rats exhibited similar increases in NPY concentrations. Reported that both NPY peptide and mRNA concentrations were increased in food-restricted rats. The present data are consistent with the recent report of with respect to NPY mRNA levels, but are not consistent with their report that NPY content is not different in Zn0 vs. Zn/ rats. However, we utilized PVN micro dissected from the hypothalamus, whereas measured levels in the whole hypothalamus. NPY content in the PVN and NPY mRNA levels in the ARC generally change in parallel, although there are a few examples of NPY content and gene expression not correlating.

CONCLUSION

The overarching conclusion is that Schedule Y had become an inadequate regulatory framework for India's clinical trial industry due to several critical shortcomings.

Ethical failures and erosion of public trust Schedule Y, despite amendments, failed to prevent widespread ethical violations, which included inadequate informed consent and the exploitation of vulnerable populations.

The lack of a robust and clear compensation mechanism for trial-related injuries or death was a major deficiency, leading to public mistrust and legal disputes.

Regulatory ambiguity and inefficiency

The regulations suffered from inconsistent reporting requirements, especially for Serious Adverse Events (SAEs), and often failed to align with global standards like those from the US Food and Drug Administration (FDA).

A lengthy and multi-tiered approval process for new drugs and trials under Schedule Y created significant delays, hindering clinical research and innovation.

Inadequate oversight and infrastructure

Schedule Y offered insufficient oversight for Ethics Committees (ECs), resulting in inconsistent enforcement of ethical standards and a lack of proper checks on investigator qualifications.

The regulatory environment under Schedule Y fostered a perception of prioritizing industry interests over patient safety, particularly after media reports of poor oversight

REFERENCES

1. Central Drugs Standard Control Organization (CDSCO). Schedule Y – Requirements and Guidelines for Clinical Trials for Import and Manufacture of New Drugs. Ministry of Health & Family Welfare, Government of India.
2. ICH E6 (R2): Good Clinical Practice: Integrated Addendum to ICH E6 (R1). International Council for Harmonisation, 2016.
3. ICH E8 (R1): General Considerations for Clinical Studies. ICH, 2021.
4. WHO. Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation. World Health Organization, 2021.
5. U.S. FDA. 21 CFR Parts 312, 314, and 50 – Clinical Trials and New Drug Applications.
6. EMA. Guideline on Advanced Therapy Medicinal Products (ATMPs). European Medicines Agency, 2020.
7. ICMR. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. Indian Council of Medical Research, 2017.
8. Ministry of Health and Family Welfare. New Drugs and Clinical Trials Rules (NDCT), 2019. Government of India.
9. Pharmacovigilance Programme of India (PvPI). Annual Performance Report, 2023.
10. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology, 2007; 132: 2087–102.
11. Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes., 2005; 29: 1153–67.
12. Buchwald H, Williams SE. Bariatric surgery worldwide 2003. Obes Surg, 2004; 14: 1157–64.
13. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med., 2004; 351: 2683–93
14. DeMaria EJ, Sugerman HJ, Meador JG, et al. High failure rate after laparoscopic adjustable silicone gastric banding for treatment of morbid obesity. Ann Surg., 2001; 233: 809–18.
15. Suter M, Calmes JM, Paroz A, Giusti V. A 10-year experience with laparoscopic gastric banding for morbid obesity: high long-term complication and failure rates. Obes Surg., 2006; 16: 829–35.
16. Suter M, Giusti V, Héraief E, Zysset F, Calmes JM. Laparoscopic Rouxen-Y gastric bypass: initial 2-year experience. Surg Endosc., 2003; 17: 603–9.
17. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg., 2000; 232: 515–29.
18. Fisher BL, Barber AE. Gastric bypass procedures. Eur J Gastroenterol Hepatol., 1999; 11: 93–7.

19. Alvarez-Leite JI. Nutrient deficiencies secondary to bariatric surgery. Curr Opin Clin Nutr Metab Care, 2004; 7: 569–75.
20. Bloomberg RD, Fleishman A, Nalle JE, Herron DM, Kini S. Nutritional deficiencies following bariatric surgery: what have we learned? Obes Surg., 2005; 15: 145–54.
21. Kluetz PG, O'connor DJ, Soltys K. Incorporating the patient experi-ence into regulatory decision making in the USA, Europe, and Canada. Lancet Oncol., 2018; 19(5): e267–e274. doi:10.1016/S1470-2045(18)30097-4
22. Thurstone LL. A law of comparative judgment. Psychol Rev., 1927; 34(4): 273–286. doi:10.1037/h0070288
23. Cutfield WS, Derraik JG, Gunn AJ, et al. Non-compliance withgrowth hormone treatment in children is common and impairs lineargrowth. PLoS One., 2011; 6(1): e16223. doi:10.1371/journal.pone.0016223
24. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treat-ments for type 2 diabetes. Eur J Health Econ., 2011; 12(3): 219–230. doi:10.1007/s10198-010-0224-8
25. Reed Johnson F, Lancsar E, Marshall D, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force Value Health, 2013; 16(1): 3–13. doi:10.1016/j.jval.2012.08.2223
26. Santhosh illendula, m. sandeep, knv rao ; Stability indicating method development and validation and simultanious estimation of dapagliflozin and saxagliptin in pharmaceutical dosage form, IAJPS, 2019; 06(07): 13791-13808. http://doi.org/10.5281/zenodo.3270622
27. Bio space. New Phase 2 data for somapacitan demonstrate its potential as an efficacious once-weekly treatment for childhood growth hormone deficiency. Published, Sept 28, 2018.
28. Santhosh illendula, N. Thirumalesh, knv rao; a validated rp-hplc method development and validation and stability studies for the simultaneous estimation of meropenem and vabrobactam in pure form and pharmaceutical dosage form, International journal of Research, April/2019; VIII(IV): 3276-3299.
29. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Jama, 2013; 309(1): 71–82. doi: 10.1001/jama.2012.113905
30. Gao F, Zheng KI, Wang X-B, Sun Q-F, Pan K-H, Wang T-Y, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care, 2020; 43(7): e72–4. doi: 10.2337/ dc20-0682
31. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev., 2020; 21(11): e13128. doi: 10.1111/obr.13128
32. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID19: A systematic review. Diabetes Metab Syn., 2020; 14(4): 655–9. doi: 10.1016/ j.dsx.2020.05.020